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INTERDEPENDENCE OF THE RADIOPROTECTIVE EFFECTS OF HUMAN RECOMBINANT INTERLEUKIN 1α, TUMOR NECROSIS FACTOR α, GRANULOCYTE COLONY-STIMULATING FACTOR, AND MURINE RECOMBINANT GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR[1]

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Interleukin 1α (IL-1α), tumor necrosis factor α (TNFα), granulocyte-colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) are molecularly distinct cytokines acting on separate receptors. The release of these cytokines can be concomitantly induced by the same signal and from the same cellular source, suggesting that they may cooperate. Administered alone, human recombinant (hr)IL-1α and hrTNFα protect lethally irradiated mice from death, whereas murine recombinant GM-CSF and hrG-CSF do not confer similar protection. On a dose basis, IL-1α is a more efficient radioprotector than TNFα. At optimal doses, IL-1α is a more radioprotective cytokine than TNFα in C57BL/6 and B6D2F$_1$ mice and less effective than TNFα in C3H/HeN mice, suggesting that the relative effectiveness of TNFα and IL-1α depends on the genetic makeup of the host. Administration of the two cytokines in combination results in additive radioprotection in all three strains. This suggests that the two cytokines act through different radioprotective pathways and argues against their apparent redundancy. Suboptimal, nonradioprotective doses of IL-1α also synergize with GM-CSF or G-CSF to confer optimal radioprotection, suggesting that such an interaction may be necessary for radioprotection of hemopoietic progenitor cells.

Cytokines are hormone-like polypeptides produced by the cells of the reticuloendothelial system after inflammatory stimuli. Ample evidence exists, based on their described in vivo and in vitro activities, that these molecules serve in host defenses against harmful exogenous challenges (1, 2). Ionizing radiation, originating from natural sources (cosmic rays), represents one such environmental hazard. Our previous observation that a cytokine, interleukin 1 (IL-1)[2] protects mice from radiation-induced death (3, 4) therefore is in accord with the concept of the role of cytokines in host defense and damage repair.

The degree of radioprotection obtained by treatment with IL-1 before irradiation resembles that previously reported for bacterial lipopolysaccharide (LPS) (5–7). Administration of LPS, however, results in induction and release of a number of cytokines, the most prominent of which are IL-1, tumor necrosis factor (TNF), and colony-stimulating factor (CSF) (8). The coordinate release of these cytokines suggests that they may act in concert. Pretreatment with human recombinant (hr) TNFα is also radioprotective, (9, 10). In contrast, we were previously unsuccessful in demonstrating radioprotection using murine recombinant (mr) granulocyte-macrophage (GM)-CSF alone (11). Furthermore, although in our hands hrIL-1 was radioprotective in five strains of mice, C57BL/6, BALB/c, DBA/1, B6D2F$_1$, and CDF$_1$, its radioprotective effect in C3H/HeN mice was minimal (12). It is possible that in the latter strain other cytokines or a combination of IL-1 with other cytokines may be more effective in radioprotection.

To evaluate the above possibilities, we have investigated the radioprotective effect of combinations of hrIL-1α and TNFα, as well as hrIL-1α and mr GM-CSF or hr granulocyte (G)-CSF. These studies were performed using C57BL/6 and B6D2F$_1$ mice, which are high responders to radioprotection with IL-1α, and C3H/HeN mice, and low responders to IL-1-mediated radioprotection.

We now report that combinations of optimally radioprotective doses of IL-1α and TNFα result in additive radioprotection in both high and low responder mice. Suboptimal doses of IL-1α in combinations with nonprotective doses of GM-CSF or G-CSF result in synergistic protection from radiation-induced death.

MATERIALS AND METHODS

Mice. C57BL/6 and B6D2F$_1$ inbred mice were obtained from The Jackson Laboratory, Bar Harbor, ME. C3H/HeN mice were purchased from Animal Genetics and Production Branch, National Cancer Institute, Frederick, MD. The mice were housed in the Veterinary Department Facility at the Armed Forces Radiobiology Research Institute in cages with Micro-Isolation unit tops, 10 mice/cage. Fe-

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[2] Abbreviations used in this paper: IL-1, interleukin 1; CSF, colony-stimulating factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; hr, human recombinant; LPS, bacterial lipopolysaccharide; mr, murine recombinant; TNF, tumor necrosis factor.

male mice 8 to 12 wk of age were used for all experiments. Standard laboratory chow and HCl-acidified water (pH 2.4) were given ad libitum. All cage-cleaning procedures and injections were carried out in a laminar flow unit.

Cytokines. The hrIL-1α was generously provided by Immunex and Hoffmann-La Roche, Nutley, NJ. The preparations were supplied in phosphate-buffered saline, pH 7.2, and 30 mM Tris-HCl, 400 mM NaCl, pH 7.8, respectively, and used on weight basis. The hrTNFα, lot CP4026POB, specific activity 9.6×10^8 U/mg in phosphate-buffered saline, was a generous gift from Biogen Research Corp., Cambridge, MA. The mrGM-CSF was provided by Immunex as a lyophilized powder with sucrose as a stabilizing agent. The hrG-CSF was a gift from Amgen, Biochemicals, Thousand Oaks, CA. Protein-free phenol-water-extracted endotoxin derived from *Escherichia coli* K235 (LPS) was obtained from Dr. S. N. Vogel, Department of Microbiology, Uniformed Services University of the Health Sciences. All reagents were diluted to the desired concentration in pyrogen-free saline just before i.p. injection of 0.5 ml/mouse. All cytokine preparations were assayed for LPS contamination in a LAL assay and determined to contain less than 0.1 ng/inoculum.

Irradiation. Mice were placed in Plexiglas containers and were given whole body irradiation at 40 rad/min by bilaterally positioned cobalt-60 elements. Mice survival was recorded daily for 30 days.

Statistical analysis. Two survival proportions were compared using a 2×2 contingency table analysis (χ^2). A survival proportion was compared with the sum of two others by assuming that survival has an exponential distribution, i.e., $\exp(-t/\lambda)$. If two survival mechanisms act independently, their mean survival was assumed to add. The survival proportion of the combined mechanism was then compared with the predicted survival proportion of the exponential sum.

RESULTS

Comparison of the radioprotective effects of hrIL-1α and hrTNFα. The effect of increasing doses of hrIL-1α and hrTNFα on the survival of $LD_{100/30}$-irradiated C57BL/6 and $LD_{95/30}$-irradiated $B6D2F_1$ mice, both high responders to radioprotection with IL-1α, was compared. C57BL/6 mice were protected with doses of IL-1α ranging from 100 to 1000 ng (Fig. 1*A*) (doses of 50 ng did not confer significant radioprotective effect; data not shown). Doses of IL-1α ranging from 75 to 1000 ng were similarly radioprotective for $B6D2F_1$ mice (Fig. 1*B*). Equivalent doses of TNFα had no radioprotective effect for these two strains. However, significant radioprotection in these two strains was obtained using 5- to 10-μg doses of TNFα (Fig. 1*A* and *B*). The maximal degree of radioprotection achieved with higher doses of TNFα, however, was less than that observed in both strains with lower doses of IL-1α ($p < 0.001$). Therefore, human TNFα is a less effective radioprotector than human IL-1α in the above two strains.

In our previous studies, C3H/HeN mice were less responsive to the radioprotective effect of IL-1α than C57BL/6, DBA/1 (12), as well as CDF_1 or BALB/c mice (R. Neta, unpublished observations). A comparison of the radioprotective effect of IL-1α and TNFα in this mouse strain showed that 5.0- to 7.5-μg doses of TNFα conferred greater protection ($p < 0.05$) than 150- to 500-ng doses of IL-1α (Fig. 1*C*). Therefore, in contrast with C57BL/6 and $B6D2F_1$ mice, TNFα is more radioprotective than IL-1α in C3H/HeN mice. However, TNFα is equally protective in all three strains (Fig. 1*A* to *C*). In doses of 0.2 μg/mouse, mrTNF did not confer protection, 0.5 μg/mouse protected 20%, 1 to 2 μg/mouse 30%, and 5 μg/mouse 40% of mice ($n = 10$ to 18 mice/group).

The radioprotective effects of the combinations of IL-1α and TNFα. The divergence of the effect of TNFα and IL-1α suggested that they may act differently. It was, therefore, of interest to determine the interactions of these two cytokines in radioprotection. The effect of combinations of IL-1α and TNFα in C57BL/6 mice was additive, as determined from the dose reductor factor (DRF) values (Fig. 2). The DRF were calculated from the ratio of $LD_{50/30}$ of IL-1 treated to control mice. Similarly, combinations of optimal doses of the two cytokines had an additive radioprotective effect ($p < 0.01$) in lethally irradiated $B6D2F_1$ mice (Table I). The radioprotective effect of IL-1α and TNFα in combination was greater in this strain than the radioprotection achieved with optimal doses of LPS ($p < 0.01$), suggesting that combinations of cytokines may be more effective radioprotectants than immunomodulatory substances that induce cytokine release.

Combinations of TNFα and IL-1α also had additive effects in low responder C3H/HeN mice at optimal doses

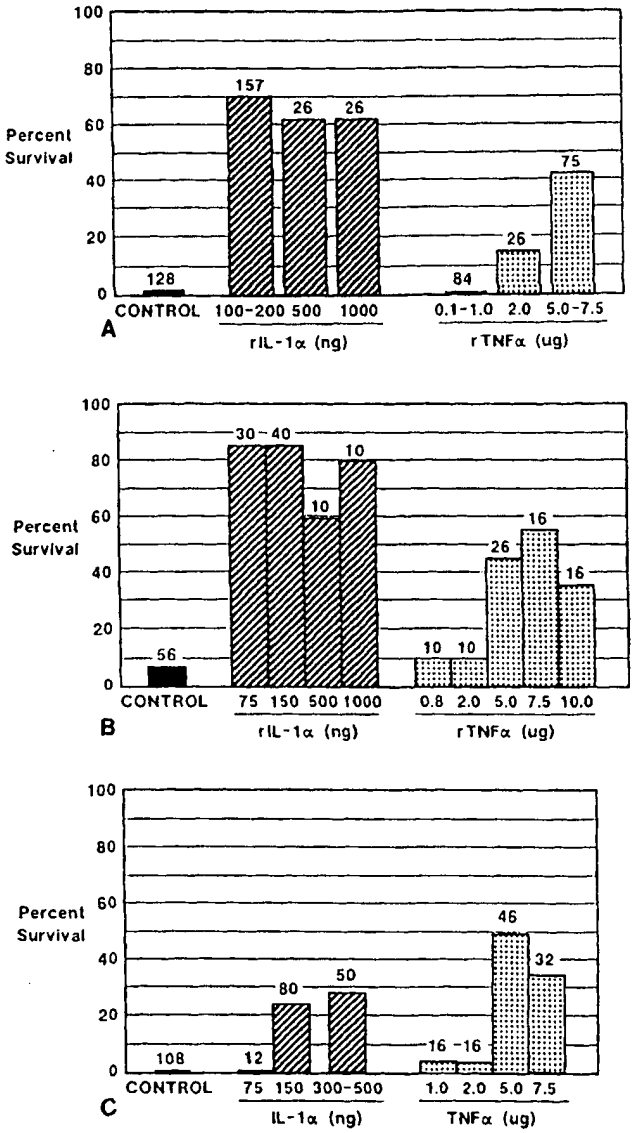

Figure 1. Protective effect of hrTNFα and hrIL-1α in lethally irradiated mice. C57BL/6 (*A*), $B6D2F_1$ (*B*), or C3H/HeN (*C*) mice, 8 to 12 wk old, received i.p. 0.5 ml saline (control) or recombinant cytokines in doses as indicated, 20 hr before whole body irradiation. The radiation doses were 950 rad ($LD_{100/30}$) for C57BL/6 (*A*), 1050 rad ($LD_{95/30}$) for $B6D2F_1$ (*B*), 850 ($LD_{100/30}$ for 8 to 9 wk old), and 900 rad ($LD_{100/30}$ for 10 to 12 wk old) C3H/HeN mice (*C*). The numbers at the top of the bars represent the total number of mice receiving each treatment. TNFα was more radioprotective than IL-1α in C3H/HeN mice ($p < 0.05$) (*C*). TNFα was less radioprotective than IL-1α in C57BL/6 and $B6D2F_1$ mice ($p < 0.001$) (*A*, *B*).

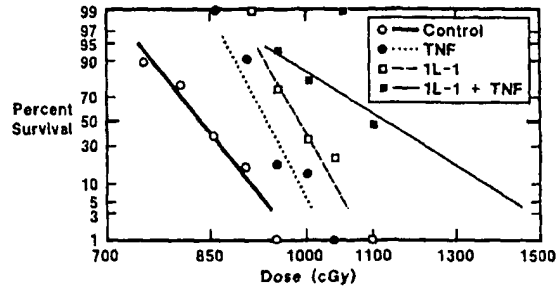

Figure 2. Radioprotective effect on hrTNFα and hrIL-1α, by themselves and in combination, in C57BL/6 mice exposed to increasing doses of radiation. C57BL/6, 8- to 12-wk-old mice, received 5 μg/mouse of hrTNFα, 150 ng/mouse of hrIL-1α, alone or in combination. Each experimental point represents 12 to 70 mice. DRF were calculated from the ratio of $LD_{50/30}$ of treated vs control mice, using probit analysis and were 1.12 (1.08, 1.16) for TNFα; 1.19 (1.16, 1.21) for IL-1α; and 1.38 (1.24, 1.54) for IL-1α + TNFα. The numbers in brackets are 95% confidence limits. Treatment with IL-1α was significantly more radioprotective than treatment with TNFα at 950 rad ($p < 0.001$) and 1000 rad ($p < 0.05$). The effect of combined treatment with IL-1α and TNFα was significantly greater than the sum of effects of treatment with IL-1α or TNFα alone at radiation doses above 1000 rad ($p < 0.01$).

TABLE I

Radioprotection of B6D2F$_1$ mice with rIL-1α, rTNFα, by themselves, and in combination[a]

Treatment	Radiation Dose			
	1050		1150	
	Dead/Total	% Survival	Dead/Total	% Survival
IL-1α				
100 ng	6/22	73	16/22	26
TNFα				
5 μg	12/22	46	21/22	6
IL-1α + TNFα				
100 ng + 5 μg	0/22	100	4/22	82
LPS				
12 μg	3/22	86	14/22	36
Saline	19/22	14	22/22	0

[a] Mice were treated as described in Figure 1. The percentage of survival of mice given 1050 or 1150 rad after treatment with IL-1α was greater than that after treatment with TNFα ($p < 0.05$). IL-1α and TNFα in combination conferred significantly greater protection than the sum of radioprotection with IL-1α and TNFα alone ($p < 0.01$) and also greater than radioprotection with optimal doses of LPS ($p < 0.01$).

TABLE II

Radioprotection of C3H/HeN mice with hrIL-1α or hrTNFα alone and in combination[a]

Treatment	Dead/Total	% Survival
Saline	175/180	2.5
IL-1α		
100 to 200 ng	78/91	15
300 to 500 ng	48/64	25
TNFα		
1.0 to 2.0 μg	32/34	6
5.0 to 7.5 μg	51/88	42
IL-1α + TNFα		
100 ng + 2.0 μg	7/16	55
200 ng + 7.5 μg	6/50	88

[a] C3H/HeN mice were treated as described in Figure 1. TNFα in doses of 5 to 7.5 μg/mouse protected significantly greater numbers of mice than treatment with 150 to 500 ng of IL-1α alone ($p < 0.05$). Treatment with IL-1α and TNFα in combination was significantly more radioprotective than the sum of the radioprotective effects of IL-1α and TNFα administered alone ($p < 0.05$).

of cytokines ($p < 0.01$) (Table II).

The effects of combinations of IL-1α with GM-CSF or G-CSF. The radioprotective effect of IL-1 occurs at radiation dose ranges that suppress hemopoiesis. It has been proposed, therefore, that the effect of IL-1 may be mediated by CSF. However, i.p. administration of GM-CSF 20 hr before irradiation in doses ranging from 1 to 10 μg/mouse had no significant protective effect against lethal doses of radiation (11). To examine further whether GM-CSF contributes to radioprotection, suboptimal doses of IL-1α were administered in combination with GM-CSF or G-CSF. Combinations of these cytokines greatly enhanced the survival of mice in comparison to the effect of each cytokine alone ($p < 0.01$) (Table III). The effect of treatment with combinations of suboptimal doses of IL-1α and GM-CSF or G-CSF equaled that achieved with optimal doses of IL-1α. This effect, however, did not extend to supralethal doses of radiation (Table III).

DISCUSSION

Inflammatory signals induce the release of various cytokines with distinct, as well as overlapping, biologic activities. IL-1α and TNFα represent two such cytokines, which are induced and released by macrophages after the same inflammatory stimulus (LPS as an example) and which also share a number of similar biologic properties, such as induction of fever (13, 14), acute phase proteins (15, 16), or CSF (17–19). Therefore, despite their differing molecular structure and their action on separate receptors, they exhibit apparent redundancy. Our results showing that the two cytokines differ in the extent of their radioprotective effect, that their relative effectiveness may vary depending on the genetic makeup of the host, and that their combined activity is additive independent of the genetic makeup argue against the apparent redundancy of these agents in this context. Higher quantities of TNFα than of IL-1α were required in all strains of mice to confer optimal radioprotection. Although most of these studies utilized hrTNFα, murine TNFα in C3H/HeN mice was also required in doses higher than IL-1 to achieve significant radioprotection.

The radioprotection achieved with optimal doses of IL-1α was greater than that with optimal doses of TNFα in C57BL/6 and B6D2F$_1$ mice, but this situation was reversed in C3H/HeN mice. TNFα, however, was equally protective in all three strains. Although we do not know the basis for the differences in protection of these inbred strains of mice, this observation suggests that different cytokines may achieve similar effects in genetically disparate individuals.

The additive effect of IL-1α and TNFα in radioprotection, independent of genetic makeup or of the dose, sug-

TABLE III

Radioprotection of B6D2F$_1$ mice with combinations of rCSF and rIL-1α[a]

Treatment	Radiation Dose			
	1050		1150	
	Dead/Total	% Survival	Dead/Total	% Survival
IL-1α				
100 ng	9/32	69	16/22	26
33 ng	34/42	19	20/22	9
GM-CSF				
1 μg	35/42	17	22/22	0
G-CSF				
1 μg	8/10	20	ND	
GM-CSF				
1 μg + IL-1α 33 ng	14/42	67	20/22	9
G-CSF				
1 μg + IL-1α 33 ng	3/10	70	ND	
Saline	35/42	17	22/22	0

[a] Mice were treated as described in Figure 1. The radioprotective effect of 33 ng IL-1α or 1 μg of GM-CSF or G-CSF did not differ significantly from treatment with saline. The effects of IL-1α and GM-CSF or IL-1α and G-CSF in combination in mice treated with 1050 rad differed significantly from controls ($p < 0.01$). ND, not determined.

gests that the two cytokines employ different radioprotective pathways. Although the mechanism of action to achieve radioprotection remains unknown, a number of the activities of IL-1α and TNFα may be related to the radioprotective effect. For example, induction of acute phase proteins, some of which (metallothionein and ceruloplasmin) have the capacity to scavenge free radicals (20–23) and other acute phase proteins, may contribute to radioprotection. Although IL-1α induction of bone marrow cell cycling (24) may present yet another critical event in radioprotection, TNFα is not known to have this capability. In fact, TNFα has been reported to be inhibitory to hemopoiesis (25, 26). Several reports exist, however, showing its role in hemopoietic differentiation (27–29). This differentiating effect is most pronounced in synergy with other cytokines. Whether this effect of TNFα on hemopoietic cells contributes to its radioprotective effect remains to be established.

The finding that treatment with TNFα and IL-1α in combination is more effective than treatment with optimal radioprotective doses of LPS (an inducer of the two cytokines) may be explained in two ways. Either the two cytokines are presented in more optimal doses than can be induced with LPS or toxic effect of the LPS molecule itself is circumvented by using the cytokines.

The lack of radioprotective effects of GM-CSF or G-CSF administered alone, and its synergistic effect when combined with suboptimal doses of IL-1α, indicate that these hemopoietic growth factors may be effective only when combined with IL-1α. Possibly, this synergy relates to the recently described hemopoietin-1 (HP-1) activity of IL-1α, because hemopoietin-1/IL-1 has been reported to synergize with GM-CSF in promoting growth of early hemopoietic progenitor cells (30). Furthermore, IL-1α has been shown to induce CSF in vitro as well as in vivo (17, 19). Thus administration of IL-1α generates cytokines with which IL-1α can interact to yield more pronounced biologic effects. Additional possibilities that need to be examined may involve induction by IL-1α of increased expression of CSF receptors.

In all, our observation that combinations of cytokines may be more effective than the administration of each cytokine alone serves as additional evidence that these agents act in concert and despite their apparent redundancy must all be required for normal host defenses.

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REFERENCES

1. **Oppenheim, J. J., and S. Cohen, eds.** *Interleukins, Lymphokines, and Cytokines.* Academic Press, New York, 1983.
2. **Adelman, N. E., M. E. Hammond, S. Cohen, and H. F. Dvorak.** 1979. Lymphokines as inflammatory mediators. In *Biology of Lymphokines.* S. Cohen, E. Pick, and J. J. Oppenheim, eds. Academic Press, New York, p. 000.
3. **Neta, R., S. D. Douches, and J. J. Oppenheim.** 1986. Interleukin 1 is a radioprotector. *J. Immunol. 136:2483.*
4. **Neta, R., S. D. Douches, and J. J. Oppenheim.** 1987. Radioprotection by interleukin-1. In *Immune Regulation by Characterized Polypeptides.* Alan R. Liss, New York, p. 429.
5. **Mefford, R. B., D. T. Henkel, and J. B. Loeffer.** 1953. Effect of pyromen on survival of irradiated mice. *Proc. Soc. Exp. Biol. Med. 83:54.*
6. **Ainsworth, E. J., and H. B. Chase.** 1959. Effect of microbial antigens on irradiation mortality in mice. *Proc. Soc. Exp. Biol. Med. 102:483.*
7. **Smith, W. W., I. M. Alderman, and R. I. Gillespie.** 1957. Increased survival in irradiated animals treated with bacterial endotoxins. *Am. J. Physiol. 191:124.*
8. **Vogel, S. N., and M. M. Hogan.** 1987. The role of cytokines in endotoxin mediated responses. In *Immunophysiology: Role of Cells and Cytokines in Immunity and Inflammation.* J. J. Oppenheim and E. Shevach, eds. Oxford University Press, New York. *In press.*
9. **Neta, R., S. N. Vogel, J. D. Sipe, J. J. Oppenheim, P. C. Giclas, and S. D. Douches.** 1987. Comparison of the in vivo effects of recombinant IL-1 and recombinant TNF in radioprotection, induction of CSF, and of acute phase reactants. *Fed. Proc. 46:1200 (Abstr.).*
10. **Urbaschek, R., D. N. Mannel, and B. Urbaschek.** 1987. Tumor necrosis factor induced stimulation of granulopoiesis and radioprotection. *Lymphokine Res. In press.*
11. **Neta, R., S. N. Vogel, J. J. Oppenheim, and S. D. Douches.** 1986. Cytokines in radioprotection: comparison of the radioprotective effects of IL-1 to IL-2, GM-CSF, and IFN-gamma. *Lymphokine Res. 5:s105.*
12. **Neta, R., S. D. Douches, and J. J. Oppenheim.** 1986. Strain dependence of mice to radioprotective effect of IL-1. *Sixth International Congress on Immunology,* Toronto, Canada, p. 448 (*Abstr.*).
13. **Kampschmidt, R. F., and H. F. Upchurch.** 1969. Some effects of endotoxin and leukocytic pyrogen on the body temperature of rats. *Proc. Soc. Exp. Biol. Med. 131:864.*
14. **Dinarello, C. A., J. G. Cannon, S. M. Wolf, H. A. Bernheim, B. Beutler, A. Cerami, I. S. Figari, M. A. Palladino, and J. V. O'Connor.** 1986. Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin-1. *J. Exp. Med. 163:1433.*
15. **Ramadori, G., J. D. Sipe, C. A. Dinarello, S. B. Mizel, and H. R. Colten.** 1985. Pretranslational modulation of acute phase hepatic protein synthesis by murine recombinant interleukin-1 (IL-1) and purified human IL-1. *J. Exp. Med. 162:930.*
16. **Sipe, J. D., S. N. Vogel, S. D. Douches, and R. Neta.** 1987. Tumor necrosis factor (cachectin) is a less potent inducer of serum amyloid A synthesis than interleukin-1. *Lymphokine Res. 6:93.*
17. **Zucali, J. R., C. A. Dinarello, D. J. Oblon, M. A. Grass, L. Anderson, and R. S. Weiner.** 1986. Interleukin-1 stimulates fibroblasts to produce granulocyte-macrophage colony-stimulating activity and prostaglandin E2. *J. Clin. Invest. 77:1857.*
18. **Munker, R., J. Gasson, M. Ogawa, and H. P. Koeffler.** 1986. Recombinant human TNF induces production of granulocyte-monocyte colony stimulating factor. *Nature 323:79.*
19. **Vogel, S. N., S. D. Douches, E. N. Kaufman, and R. Neta.** 1987. Induction of colony stimulating factor in vivo by recombinant interleukin-1 and tumor necrosis factor. *J. Immunol. 138: 2143.*
20. **Goldstein, I. M., and I. F. Charo.** 1983. Ceruloplasmin: an acute phase reactant and antioxidant. In *Lymphokines.* E. Pick, ed. Academic Press, New York, *8:383.*
21. **Karin, M., R. J. Imbra, A. Heguy, and G. Wong.** 1985. Interleukin-1 regulates human metallothionein gene expression. *Mol. Cell. Biol. 5:2866.*
22. **Thornalley, P. J., and M. Vajak.** 1985. Possible role for metallothionein in protection against radiation induced oxidative stress; kinetics and mechanism of its reaction with superoxide and hydroxyl radicals. *Biochim. Biophys. Acta 827:36.*
23. **Neta, R., J. J. Oppenheim, S. D. Douches, P. C. Giclas, R. I. Imbra, and M. Karin.** 1986. Radioprotection with interleukin-1: comparison with other cytokines. In *Progress in Immunology. VI.* B. Cinader and R. G. Miller, eds. Academic Press, New York, p. 900.
24. **Neta, R., M. B. Sztein, J. J. Oppenheim, S. Gillis, and S. D. Douches.** 1987. The in vivo effects of interleukin 1. I. Bone marrow cells are induced to cycle after administration of interleukin 1. *J. Immunol. 139:1861.*
25. **Peetre, C., U. Gullberg, E. Nilsson, and I. Olsson.** 1986. Effects of recombinant tumor necrosis factor on proliferation and differentiation of leukemic and normal hemopoietic cells in vitro. *J. Clin. Invest. 78:1694.*
26. **Murase, T., T. Hotta, H. Saito, and R. Ohno.** 1987. Effect of recombinant human tumor necrosis factor on the colony growth of human leukemia progenitor cells and normal hematopoietic progenitor cells. *Blood 69:467.*
27. **Trinchieri, G., M. Kobayashi, M. Rosen, R. Loudon, M. Murphy, and B. Perussia.** 1986. Tumor necrosis factor and lymphotoxin induce differentiation of human myeloid cell lines in synergy with immune interferon. *J. Exp. Med. 164:1206.*
28. **Munker, R., and P. Koeffler.** 1987. In vitro action of tumor necrosis factor on myeloid leukemic cells. *Blood 69:1102.*
29. **Takeda, K., S. Iwamoto, H. Sugimoto, T. Takuma, N. Kawatani, M. Noda, A. Masaki, H. Morise, H. Arimura, and K. Konno.** 1986. Identity of differentiation inducing factor and tumor necrosis factor. *Nature 323:338.*
30. **Moore, M. A. S., and D. J. Warren.** 1987. Synergy of interleukin-1 and granulocyte colony stimulating factor: in vivo stimulation of stem cell recovery and hematopoietic regeneration following 5-fluorouracil treatment of mice. *Proc. Natl. Acad. Sci. USA 84:7134.*